

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: John Moon	:
	: Art Unit: 1743
Serial No.: 10/661,836	:
	: Examiner: Hyun, Paul Sang Hwa
Filed: September 12, 2003	:
	:
For: METHOD AND APPARATUS FOR	:
ALIGNING MICROBEADS IN ORDER TO	:
INTERROGATE THE SAME	:
	:
	:

**AMENDMENT**

Mail Stop: AMENDMENT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

In response to the Office Action dated September 20, 2007, Applicant respectfully requests consideration and entry of the following amendment:

**EXHIBIT A**

IN THE SPECIFICATION:

Please amend the CROSS REFERENCE TO RELATED APPLICATION paragraphs at page 1, lines 5-10, as follows:

This application claims the benefit of US Provisional Patent Applications, Serial No. 60/410,541 (~~CiDRA Docket No. CC-543~~), filed Sept. 12, 2002, and is a continuation-in-part of US Patent Applications, Application Serial No. 10/645,689, (~~CiDRA Docket No. CC-0648~~), filed Aug. 20, 2003, each of which are incorporated herein by reference in their entirety.

US Patent Application Serial No. (~~CiDRA Docket No. CC-0648A~~) 10/661,234 and Application Serial No. (~~CiDRA Docket No. CC-0650~~) 10/661,082, filed contemporaneously herewith, ~~contains~~ contain subject matter related to that disclosed herein, which is incorporated by reference in its entirety.

IN THE CLAIMS:

1. (Currently Amended) A method for aligning microbeads to be read by a code reading or other detection device, comprising:

providing microbeads to a positioning device, each microbead having an elongated body with a holographic code embedded-disposed thereon or therein, the code being oriented to extend along a longitudinal axis of the corresponding microbead; and

aligning the microbeads with the positioning device so the codes and longitudinal axis of the microbeads are in a common fixed orientation relative to the code reading or other detection device.

2. (Currently Amended) A method according to claim 1, wherein the positioning device ~~is~~includes a plate having a multiplicity of grooves therein, the microbeads being aligned in the grooves such that the longitudinal axis of the microbeads extends along a length of the corresponding groove.

3. (Currently Amended) A method according to claim 2, wherein the method includes agitating the plate to encourage ~~the~~alignment of the microbeads into the grooves.

4. (Currently Amended) A method according to claim 1, wherein the microbeads are ~~cylindrically-tubularly shaped glass beads between 25 and 250 microns in~~with a length extending along the longitudinal axis and with a circular diameter and between 100 and 500 microns longtraversing the longitudinal axis, the length being greater than the diameter.

5. (Currently Amended) A method according to claim 1, wherein the microbeads have a ~~the~~holographic code embedded in a central region thereof.

6. (Original) A method according to claim 1, wherein the code is used to correlate a chemical content on each bead with a measured fluorescence signal.

7. (Currently Amended) A method according to claim 1, wherein the elongated body has opposite ends arranged along the longitudinal axis and sides located transversely with respect to the longitudinal axis, the positioning device holding each microbead is in a substantially aligned known fixed orientation and alignment in relation to its pitch and yaw rotational axes an end to end pitch direction and a side to side yaw direction while permitting the microbeads to rotate in a roll direction about the longitudinal axis.

8. (Currently Amended) A method according to claim 1, wherein the plate has a series of parallel grooves having one of ~~several different shapes, including~~ a square shape, a rectangular shape, v-shaped or and semi-circular shape.

9. (Currently Amended) A method according to claim 2, wherein the plate is an optically transparent medium including boro-silicate glass, fused silica or plastic, and the grooves are ~~formed therein~~ open sided.

10. (Currently Amended) A method according to claim 2, wherein the microbeads have a ~~circular dimension and~~ tubular shape with a circular cross-section and are positioned end to end in the grooves, the grooves have having an open side with a depth that is dimensioned to be at least the a diameter of the microbeads, including at least 110% of the diameter of the microbead.

11. (Previously Presented) A method according to claim 2, wherein the microbeads have a circular dimension and either the grooves have a depth between 10 and 125 microns, the depth is dimensioned within 90% of the diameter of the microbeads, or a combination thereof.

12. (Previously Presented) A method according to claim 2, wherein the microbeads have a circular dimension and a spacing of the grooves is between 1 and 2 times the diameter of the microbeads.

13. (Currently Amended) A method according to claim 2, wherein the grooves have an open side and the microbeads, when introduced, are free to move across a side of the plate until aligning with and coming to rest in the grooves ~~a width that is dimensioned to prevent the beads from rotating therein by more than a few degrees.~~

14. (Currently Amended) A method according to claim 2, wherein the microbeads have a ~~circular dimension~~ tubular shape and the grooves have ~~a width that is dimensioned within 5% of the diameter of the microbeads~~ are arranged in one of rows, concentric circles and spirals.

15. (Previously Presented) A method according to claim 2, wherein the grooves have a bottom that is flat enough to prevent the beads from rotating, by more than a few tenths of a degree, relative to the code reader device.

16. (Original) A method according to claim 1, wherein the code reader device includes a readout camera.

17. (Previously Presented) A method according to claim 2, further comprising agitating the plate using a sonic transducer, a mechanical wipe, or shaking or rocking device.

18. (Withdrawn) A method according to claim 1, wherein the method includes using an open format approach by dispensing the microbeads onto the plate using a pipette tip or syringe tip and not covering the plate.

19. (Currently Amended) A method according to claim 1, ~~wherein the method includes a closed format approach by~~ further comprising dispensing the microbeads into a cuvette-like device comprising ~~the~~ a plate, at least three walls and a cover.

20. (Currently Amended) A method according to claim 19, wherein the step of dispensing includes injecting the microbeads near an edge of an opening into the cuvette-like device ~~by placing them near an edge of an opening~~ and allowing the surface tension, or an induced fluid flow, to pull the microbeads into the cuvette-like device.

21. (Currently Amended) A method according to claim 19, wherein the method includes using a closed format approach by sectioning a closed region into two regions, a first region where the microbeads are free to move about in a plane, either in a groove or not, and a second region where the microbeads are trapped in a groove and can only move along ~~the axes~~ an axis of the grooves.

22. (Original) A method according to claim 21, wherein the method includes the step of trapping the microbeads in a groove by reducing the height of the closed region so that the microbeads can no longer come out of the groove.

23. (Original) A method according to claim 21, wherein the first region is used to pre-align the beads into a groove, facilitating the introduction of beads into the second region.

24. (Currently Amended) A method according to claim 21, wherein the method includes tilting the cuvette-like device up so gravity can be used to pull the microbeads along a groove from the first region to the second region.

25. (Original) A method according to claim 21, wherein the plate is made of silicon having walls formed by Su8 coupled thereto, or having walls formed by etching the silicon.

26. (Original) A method according to claim 1, wherein the method includes the step of identifying a chemical content on the surface of the microbead with a measured fluorescence signal.

27. (Original) A method according to claim 1, wherein the method includes passing a code reading signal through the microbead aligned on the positioning device.

28. (Original) A method according to claim 1, wherein the method further includes the step of correlating a chemical content identified on each microbead with a fluorescence signal, including one provided by an incident laser beam device.

29. (Original) A method according to claim 1, wherein the method includes the step of identifying the code in the microbead.

30. (Previously Presented) A method according to claim 2, wherein the grooves of the plate are formed using a photo lithographic process.

31. (Previously Presented) A method according to claim 2, wherein the plate includes a glass plate having Su8 thereon.

32. (Previously Presented) A method according to claim 31, wherein the glass plate is a low fluorescence glass.

33. (Withdrawn) A method according to claim 1, wherein the glass plate is a boro silicate glass.

34. (Previously Presented) A method according to claim 2, wherein the grooves on the plate are mechanically machined.

35. (Withdrawn) A method according to claim 1, wherein the grooves on the plate are formed by deep reactive ion etching.

36. (Withdrawn) A method according to claim 1, wherein the grooves on the plate are formed by injection molding.

37. (Original) A method according to claim 2, wherein the plate has a mirror coating.

38. (Original) A method according to claim 2, wherein the plate is a disk having circumferential grooves, concentric grooves, or a combination thereof.

39. (Withdrawn) A method according to claim 2, wherein the plate is a disk having radial grooves.

40. (Original) A method according to claim 2, wherein the plate is a disk having a microbead loading area located in the center of the disk.

41. (Original) A method according to claim 2, wherein the plate is a disk having one or more radial water channels extending from the center to the outer periphery thereof.

42. (Original) A method according to claim 2, wherein the method includes arranging the plate on a rotating disk.

43. (Withdrawn) A method according to claim 1, wherein the positioning device is a flow tube.

44. (Withdrawn) A method according to claim 43, wherein the step of providing includes providing the microbeads to the flow tube in a fluid.

45. (Currently Amended) A method according to claim 1, wherein the positioning device comprises a plurality of holes that receive the microbeads ~~have tubular holes extending therethrough~~.

46. (Original) A method according to claim 1, wherein the microbeads have teeth or protrusions thereon.



47. (Currently Amended) An apparatus for aligning microbeads to be read by a code reading device, comprising:

a positioning device for aligning microbeads, each microbead having an elongated body with a holographic code-embedded disposed thereon or therein, the code being oriented to extend along a longitudinal axis of the corresponding microbead, so the codes and the longitudinal axis of the microbeads are positioned-held in the positioning device in a common fixed orientation relative to the code reading device.

48. (Currently Amended) The apparatus according to claim 47, wherein the positioning device is-including a plate having a multiplicity of grooves therein, the microbeads being aligned in the grooves such that the longitudinal axis of the microbeads extends along a length of the corresponding groove.

49. (Currently Amended) The apparatus according to claim 48, wherein the apparatus includes means for agitating the plate to encourage the alignment of the microbeads into the grooves.

50. (Previously Presented) The apparatus according to claim 47, wherein the microbeads are cylindrically shaped glass beads between 25 and 250 microns in diameter and between 100 and 500 microns long.

51. (Currently Amended) The apparatus according to claim 47, wherein the microbeads have a-the holographic code embedded in a central region thereof.

52. (Withdrawn) Apparatus according to claim 47, wherein the positioning device is a rotating disk having a multiplicity of circumferential grooves, concentric grooves or a combination thereof formed therein, or having one or more spiral grooves.

53. (Withdrawn) Apparatus according to claim 47, wherein the positioning device is a tube.

54-57. (Cancelled)

58. (New) A method for aligning microbeads to be read by a code reading or other detection device, comprising:

providing microbeads to a positioning device, wherein the positioning device comprises a groove plate with a side having a multiplicity of grooves therein to receive the microbeads, each microbead having an elongated body with a code disposed thereon or therein, the code being oriented to extend along a longitudinal axis of the corresponding microbead;

causing the microbeads to flow freely across the side of the groove plate; and

aligning the microbeads with the positioning device by moving the groove plate to cause at least a portion of the microbeads to align within the grooves so the codes and longitudinal axis of the microbeads are in a fixed orientation relative to the code reading or other detection device.

59. (New) The method of claim 1, wherein the holographic code is defined at least in part by variation of refractive index of the microbead, the refractive index varying in an axial direction along the longitudinal axis of the microbead.

60. (New) The method of claim 1, wherein the holographic code comprise a numeric code formed from a series of bits arranged proximate one another along the longitudinal axis of the microbead, each of the bits being assigned one of at least two values.

## REMARKS

Claims 1-57 were pending in the present application, from which claims 18, 33, 35, 36, 39, 43, 44 and 52-57 have been withdrawn from consideration. By this amendment, claims 54-57 have been cancelled and new claims 58-60 have been added. It is respectfully submitted that the pending claims define allowable subject matter.

Regarding the obviousness type of double patenting rejections, it is believed that the claims limitations discussed hereafter, in connection with the cited art, are patentably distinct from the claims of the co-pending applications 11/063,665 and 11/226,892. Applicants reserve the right to file a terminal disclaimer at a later time should it be desirable to do so to expedite prosecution.

Regarding the indefiniteness rejection of claims 8 and 19-25, the above claim amendments are believed to address the antecedent basis issues raised in the Office Action and thus overcome the indefiniteness issues.

Turning to the substantive rejections, claims 1, 4, 6, 7, 16, 26-29, 47, 50 and 51 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Ravkin et al (USP 6,908,737). Claims 47-49 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Boulton et al (USP 6,027,694). Claims 2, 3, 9-15, 17, 30-32, 34, 37, 38 and 40-42 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ravkin in view of Seul (US 2003/0082587). Claim 5 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ravkin in view of Spencer (US 6,242,056). Claims 45 and 46 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ravkin in view of Ravkin (US 2003/0129654). Applicants respectfully traverse these rejections for reasons set forth hereafter.

First it is respectfully submitted that the cited art fails to teach or suggest the method of claim 1 and apparatus of claim 47. Claim 1 recites, among other things, providing microbeads having an elongated body with a holographic code disposed therein or thereon. The code is oriented to extend along a longitudinal axis of the microbead. The method further comprises aligning the microbeads with a positioning device so the codes and the longitudinal axis of the microbeads are in a common fixed orientation

relative to the code reader or other detection device. Claim 47 recites an aligning apparatus having similar elements to those of claim 1.

Ravkin '737 fails to teach or suggest any such alignment apparatus and method. Ravkin '737 discusses various encoded carrier chip arrangements that use color coding to form different codes. The color codes are arranged in various manners. Ravkin '737 does not discuss orientation of the color codes relative to the axis of a microbead. Also, Ravkin '737 provides no reason to align a code in any particular orientation relative to the axes of a microbead, let alone aligning the code and longitudinal axis in a common fixed relation.

Further, as noted in the outstanding Office Action, at page 8, Ravkin '737 does not disclose the use of holographic codes. The Office Action alleges, in connection with the rejection to claim 5, that Spencer discloses holographic codes and as such it would have been obvious to one of ordinary skill to provide holographic codes on the microbeads of Ravkin. The undersigned strenuously disagrees. There is no legitimate reason to provide the claimed holographic code in place of Ravkin's color codes.

Spencer concerns an unrelated and entirely different field, namely processes for applying light emission enhanced microbead paint compositions to automobiles, boats, aircraft and home appliances. Spencer discusses glass bead paint containing color enhancers that provide rich deep automobile body colors and high specular flash or light scattering when viewed directly, as well as a translucent rich deep elegant contrast when viewed at an angle, such as on contoured body surfaces of an automobile (column 5, lines 42-50). Spencer's microbeads are intended for use in paints for automobiles, boats, airplanes, appliances, hazard signs, road signs, emergency vehicles and the like (column 4, lines 42-54). In contrast, Ravkin describes systems and methods for conducting multiplexed detection and quantification of analytes for biomedical discovery, such as drug development, genome analysis and diagnostics. The carriers of Ravkin '737 are used in multiplexed genome analysis with nucleic acid arrays. The color codes identify different chemical compounds carried on each coded carrier (column 4, lines 11-17). Ravkin's and Spencer's fields of use, problems to be solved and specific embodiments fundamentally differ from one another and as such are related to non-analogous arts. The person of ordinary skill in the art pertaining to the claimed invention would have no

legitimate reason to modify Ravkin's color coded carrier based upon Spencer's paint compositions for a vehicle.

Moreover, it is respectfully submitted that Spencer's discussion at column 3, line 38 has been misinterpreted in the Office Action. In the Office Action, it is suggested that Spencer discloses microbeads comprising holographic codes as means to identify the microbeads. This is not a fair characterization of Spencer's teaching. Spencer states the following:

The most critical component of the present light transmissive compositions is the mixture of color enhancers and microbeads which comprises (a) translucent, preferably optically-clear, light-refracting microbeads; and (b) one or more color-enhancing additives such as reflective microbeads which are coated with or encapsulate a reflective material, such as aluminum beads or aluminum-coated glass microbeads, or which are coated with or encapsulate colored dye or pigment or luminescent or phosphorescent materials, or consist of pigments, dyes, metal flake, mica or holographic flake, to lend color, depth and intensity to the paint coatings (column 3, lines 28-39).

When the pertinent discussion of Spencer is understood in context, it is clear that Spencer does not suggest to use holographic codes as a means to identify microbeads as claimed. Instead, Spencer lists holographic flakes, among a variety of other items, as a way to lend color, depth and intensity to paint coatings. This further emphasizes the differences and divergence between the teachings of Spencer and Ravkin. A person of ordinary skill in the art pertaining to the claimed invention would not have found any motivation, based upon Spencer's holographic flakes, to so fundamentally modify Ravkin's systems and methods of conducting multiplexed experiments of analytes. Thus, the cited art fails to teach or suggest the claimed microbead structure for use in a method and apparatus for aligning microbeads.

Further, Applicants traverse the anticipatory rejection of claim 47 based upon Boulton. Boulton does not align microbeads having the claimed code structure. Nor does Boulton hold microbeads in a positioning device with codes and longitudinal axes in a common fixed orientation. Instead, Boulton describes a microplate assembly 10 with wells 17 that receive liquid samples 19.

Moreover, it is submitted that the dependent claims and new claims recite several patentably distinct features.

Turning to claims 2 and 48, it is submitted that the cited art fails to teach or suggest the claimed positioning device which includes a plate having a multiplicity of grooves therein, where each of the microbeads are aligned in the grooves such that the longitudinal axis of the microbeads extends along a length of a corresponding groove. At page 7 of the Office Action, it is conceded that Ravkin '737 does not disclose a plate comprising grooves. Yet the Office Action alleges that it would have been obvious to form the array of microbeads disclosed by Ravkin '737 on a chip similar to the one disclosed by Seul as Seul's chip would provide a substrate on which an array of microbeads could be securely arranged.

There is no legitimate reason to modify Ravkin's fixed array 1300 (Figure 13) based upon the teachings of Seul. Ravkin '737 describes, in connection with the embodiment of Figure 13, a fixed array 1300 that contains carriers 1306 fixedly organized in the interior geometry of the array organizer 1301. The array organizer 1301 has an inlet 1302 and outlet 1303. The organizer 1301 receives the carriers 1306 through the inlet 1302 and discharges the carriers 1306 from the outlet 1303.

There is no reason to replace the organizer 1301 with a chip layout as described by Seul. Seul describes exemplary chip layouts in paragraphs 51-53 (cited in the outstanding Office Action) that are fundamentally different and would not be practical to implement with, or in place of, the organizer 1301 of Ravkin. Ravkin's organizer 1301 provides an enclosed container that is temporarily filled with carriers 1306 before the carriers are exhausted from the output 1303. In contrast, Seul describes a chip layout having a substrate L1 where bio-functionalized beads are assembled to form an array of micro-particles. A recessed array A1 of L1 is where the bead array is built. The recess array A1 arranges and secures the beads by building rectangular structures on the wafer or chip to confine the movement of the beads on the surface. However, Seul's chip layout is intended for use when building a bead array, whereas in Ravkin, it is expected that the carriers 1306 have previously been built before being loaded into the organizer 1301. Also, in Seul, the bead array is surrounded by a significant amount of unused space, as is evident in Figures 2 and 3, whereas in Ravkin, the organizer is configured to densely pack the carriers 1306 against one another in order to minimize dead volume (column 19, lines 1-5 of Ravkin). Thus, when the true teachings of Seul and Ravkin are

considered, it is clear that there is no legitimate reason to replace Ravkin's organizer 1301 with a plate having the claimed structure.

Regarding claims 3 and 17, it is submitted that the Office Action fails to establish a prima facie case of obviousness based on the combined teachings of Ravkin '737 and Seul. Claim 3 provides that the plate with the multiplicity of grooves is agitated to encourage alignment of the microbeads into the grooves. Claim 17 recites particular operations for agitation. The Office Action implicitly acknowledges that Ravkin '737 fails to teach agitating a groove plate. Yet the Office Action maintains that it would have been obvious to manually agitate or position Ravkin's modified chip on rotating disc to encourage the microbeads to align in the features. However, no secondary reference is cited as establishing a reason for making the alleged modification to Ravkin '737. Hence, the Office Action is deficient and has not established a prima facie case of obviousness as it has not established any reason within the cited art to make the alleged modification. In the event that the Examiner is taking Official Notice with respect to the basis for the obviousness rejection of claims 3 and 17, the Examiner is requested to provide a publication or other factual evidence establishing the basis for the alleged reason to make the modification.

It is further submitted that Official Notice is an improper means upon which to rely for this claimed feature, particularly in view of the fact that the modification suggested is not simply to the base structure of Ravkin '737. Instead, the obviousness rejection maintains that it would have been obvious to replace Ravkin's original organizer 1301 with a chip layout of Seul and then make the further modification to the alleged combination of Ravkin '737 and Seul, to provide manual agitation or positioning on a rotating disc. Significantly, Ravkin's original organizer 1301 did not use, nor need, manual agitation nor a rotating disc. Similarly, Seul's chip layout did not utilize, nor need, manual agitation or a rotating disc. Hence, the reliance on Official Notice and the obviousness rejection are improper.

Regarding claim 7, the cited art fails to teach or suggest a positioning device that maintains microbeads in the claimed fixed orientation and alignment in relation to an end-to-end pitch direction and a side-to-side yaw direction of the microbead, while simultaneously permitting the microbeads to rotate in a roll direction about the

longitudinal axis. In Ravkin, the organizer 1301 is an open chamber and does not limit movement of the carrier 1306 in any of the pitch, yaw and roll directions, while the chip layout in Seul maintains the bead array in a secure position in 3D space and does not permit movement with respect to any direction.

Regarding claim 14, the cited art fails to teach or suggest the use of tubular shaped microbeads and grooves that are arranged in one of rows, concentric circles and spirals. Seul's chip layout does not include any of the claimed groove structures, nor does Ravkin's organizer 1301.

Regarding the rejections of claims 38, 40 and 41, it is submitted that the Office Action fails to establish a prima facie case of obviousness. The teachings of Seul do not make up for the deficiencies of Ravkin in a manner that render obvious the additional limitations of such claims. Claim 38 further defines the plate to include a disc having circumferential grooves, concentric grooves or a combination thereof. Claim 40 further defines the plate to have a disc with a microbead loading area located in the center of the disc, while claim 42 further defines the plate to be a disc having one or more radial water channels extending from the center to the outer periphery thereof. The Office Action cites to paragraph 53 of Seul for the alleged proposition that Seul discloses that the features on the disc can be any shape that can confine movement of microbeads. From this statement, the Office Action extrapolates that the person of ordinary skill would have found it obvious to make the claimed disc structure. The teachings of Seul fall far short of anything remotely resembling a suggestion to provide a disc with the claimed structure. Paragraph 53 of Seul, is merely a portion of a discussion of an exemplary chip layout as shown in Figure 2 of Seul. The particular shape illustrated in Figure 2 is reproduced hereafter.



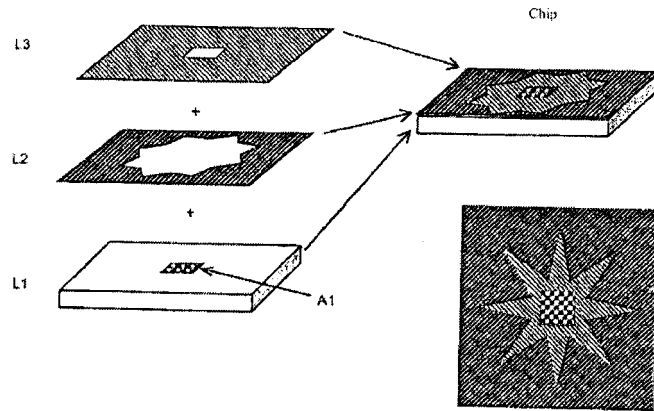


Fig. 2

Seul provides in paragraph 53 that the shape of recesses A1 need not be square, but instead “non-limiting examples of other suitable shapes include triangles, rectangles, pentagons, hexagons, and circles.” This general statement by Seul of potential shapes for the recess A1, fall far short of a sufficient reason that would lead one of ordinary skill to modify Ravkin in a manner to provide a disc with the claimed structure.

Further, Seul’s recess area A1 is a single shape without any grooves therein. Hence, even assuming arguendo that the recessed area A1 were formed as a circle, this would not lead one of ordinary skill to add the additional limitations of the claims of interest, namely circumferential grooves, concentric grooves, a combination thereof, a microbead loading area located in the center of a disc, one or more radial water channels extending from the center to an outer periphery of a disc, and the like. Hence, the outstanding Office Action has failed to establish a prima facie case of obviousness with respect to claims 38, 40 and 41.

As to claim 48, Boulton’s microplate structure 11, vent caps 12 and vent film 13 do not include a plate with the claimed structure that holds microbeads in the claimed manner.

The published application of Ravkin ‘654 fails to make up for the deficiencies noted above. Ravkin ‘654 and Ravkin ‘737 claim priority to certain common parent applications. While the disclosures of Ravkin ‘654 and Ravkin ‘737 are not identical, they are substantially similar with respect to the relevant portions of their teachings and suggestions.

In view of the foregoing comments, it is respectfully submitted that the cited references fail to teach or suggest the claimed invention. Should anything remain in order to place the present application in condition for allowance, the Examiner is kindly invited to contact the undersigned at the telephone number listed below.

Respectfully Submitted,

Date: November 30, 2007

A handwritten signature in cursive script that reads "Dean Small". The signature is written in dark ink and is positioned above a horizontal line.

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